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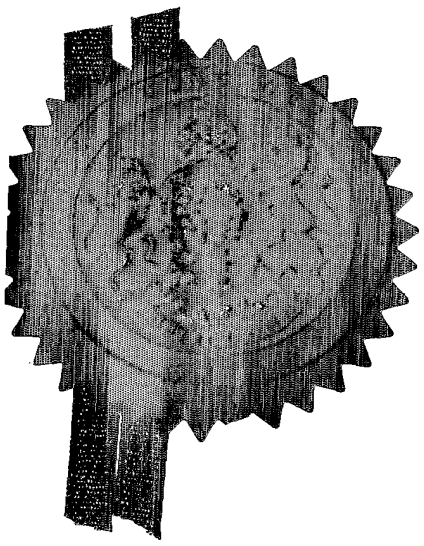

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Dated 28 April 2005

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# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

13 APR 2004

1. Your reference **P103.GB.BIOSTAB**

2. Patent application number *(The Patent Office will fill in this part)* 0408199.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

**CAMBRIDGE BIOSTABILITY LIMITED,**
**NIAB,**
**HUNTINGTON ROAD,**
**CAMBRIDGE,**
**CAMBRIDGESHIRE**
**CB3 0LE**

Patents ADP number *(if you know it)* 08847766001

If the applicant is a corporate body, give the country/state of its incorporation **ENGLAND AND WALES**

4. Title of the invention

LIQUIDS CONTAINING SUSPENDED SUGAR GLASS PARTICLES

5. Name of your agent *(if you have one)* **Roger Tolfree**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

**Tolfree Patents & Trademarks**
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Patents ADP number *(if you know it)* **08676223001** ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body*
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**YES**

**Patents Form 1/77**

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| Continuation sheets of this form | - |
| Description | 5 |
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| Priority documents | - |
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| Statement of inventorship and right to grant of a patent (Patents Form 7/77) | - |
| Request for preliminary examination and search (Patents Form 9/77) | - |
| Request for substantive examination (Patents Form 10/77) | - |
| Any other documents *(please specify)* | - |

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 13 APRIL 2004

12. Name and daytime telephone number of person to contact in the United Kingdom **Roger Tolfree 01354 680730**

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# LIQUIDS CONTAINING SUSPENDED SUGAR GLASS PARTICLES

This invention relates to a formulation comprising an active ingredient preserved in particles of a glassy or amorphous substance suspended in a liquid.

It is well known that sugar glass has an ability to preserve certain organic, biological, botanical and protein materials and there is a considerable amount of literature devoted to theoretical proposals for using this property of sugar glass to preserve pharmaceutical products, particularly vaccines. Other glassy substances have been shown to have a similar preservative effect.

Because the most commonly accepted method of administering vaccines is by injection it has been proposed, eg in patent specification .....(Roser) to suspend particles of sugar glass, containing the vaccine, in a liquid (a perfluorocarbon such as perfluorodecalin) so as to create an injectable formulation. Perfluorocarbons were proposed because they are very stable and know as being safe for pharmaceutical and medical uses. Later, it was proposed in patent specification..... to increase the density of the glass by adding calcium phosphate (density about 2.7 to 2.8) to the sugar glass (density about 1.5) so as to produce particles matched to the 1.97 density value of the liquid in which they were to be suspended; so as to keep them in suspension.

The above techniques, whilst showing great promise, have not het been proven to be capable of producing a formulation in which the particles remain in suspension over a period of time. It has beenwas assumed that this is because the calcium phosphate is not distributed evenly within the sugar glass and a certain amount of research has been conducted by the inventors to investigate ways of avoiding this problem.

According to this invention there is provided a formulation comprising an active ingredient preserved in glassy or amorphous particles, the particles being suspended in a liquid comprising a hydrofluoroether.

The inventors discovered that when sugar glass particles were added to a hydrofluoroether, they dispersed astonishingly easily to form a milky solution with no signs of clumping of the glass particles even after the suspension had been left for some time.

The inventors have now developed the theory that the glass particles have a hydrophilic surface whilst the perfluorocarbons, previously used, are hydrophobic. For this reason, in the earlier experiments with perfluorocarbons, it is now believed that the glass particles had a tendency to clump together because they are repelled by the perfluorocarbon. The hydrofluoroethers, being slightly more reactive than perfluorocarbons, behave somewhat like a detergent, facilitating dispersion of the particles.

Hydrofluorethers (HFEs) have been developed for use in cleaning electronic components and for that purpose their density, and to some extent their toxicity, is irrelevant. However it so happens that they are highly non-toxic and their densities are ideally matched to the densities of glasses used in the formulations described above. For example, referring to the designations of 3M Limited:

HFE 7500 has a density of 1.6,

HFE 7200 has a density of 1.4, and

HFE 7100 has a density of 1.5.

These values are, co-incidentally similar to the density of sugar glass, which is about 1.5.

An additional benefit of using the invention is that HFEs, whilst being highly stable in normal conditions, are unstable when exposed to strong ultraviolet radiation such as is present in the stratosphere. This avoids a problem associated with perfluorocarbons which are known to contribute to the damaging "greenhouse" effect when released into the atmosphere after use.

Yet another advantage of the invention is that HFEs are relatively inexpensive and are readily available at a high degree of purity, greater than 98%. This

compares with PFCs for which a typical example might have a purity of only about 55%.

Because the HFEs are so well matched with the glasses, it has become possible to adopt a completely new approach to density matching. Previously, the glass was formulated, by use of additives, to match its density to that of the liquid PFC. However, it now becomes unnecessary to constrain the selection of the glass according to the need to achieve the correct density. The invention makes it possible to select the ideal glass/active ingredient composition; and then to mix HFEs possibly with the addition of small quantities of PFCs or other liquids so as to match the density of the liquid to the density of the particles. It even becomes practicable to take ready-made compositions of active ingredient preserved in lumps of a glassy substance; to grind it into particles and then to suspend it in a liquid matched to the density of the particles.

The densities of the particles and of the liquid do not have to be identical. However they should be sufficiently close that Brownian movement or other influences should keep the particles in suspension. The required closeness of the densities will normally be related to the size of the particles because small particles are more easily held in suspension.

Because the particles have been found to disperse so effectively in the HFEs, the need to make the particles as small as possible, to maintain a suspension, is

now not as acute as before. Spray drying, which was previously thought by the inventors to be necessary in order to achieve small particle size, is still one possible technique for making the particles. However alternative methods such as freeze drying or grinding would now also be practicable. It is only necessary that the particles should be sufficiently small to permit passage through a hypodermic syringe.

It is envisaged that the invention will normally be employed for the formulation of vaccines or other medications for injection through the skin of a patient. However other uses for the invention may be possible, eg for medicinal liquids which are administered orally or inhaled after atomising. It is also possible that there may be non-medicinal uses for the invention which is generally applicable to any situation where it is desired to preserve a biologically active material in a glassy solid and where there is a need for the composition to be presented in liquid form.

CLAIMS

1. A formulation comprising an active ingredient preserved in glassy or amorphous particles, the particles being suspended in a liquid comprising a hydrofluoroether.

2. A formulation according to Claim 1 in which the particles contain a sugar glass.

3. A formulation according to Claim 1 or 2 in which the particles have a density which is matched to the density of the liquid sufficiently closely that the particles will remain in suspension under normal conditions.

4. A formulation according to any preceding claim in which the liquid contains different hydrofluoroethers mixed in proportions to give a required density.

5. A formulation according to any preceding claim in which the liquid contains a perfluorocarbon mixed with one or more perfluoroethers.

6. A formulation according to any preceding Claim in which the active ingredient is a vaccine.

7. A formulation according to any preceding Claim in which the particles are made by spray drying

8. A formulation according to any one of claims 1 to 6 in which the particles are made by freeze drying.

9. A formulation according to any one of claims 1 to 6 in which the particles are made by grinding.

7. A method of making a formulation according to Claim 4 or 5 including the step of selecting liquids to give the required density matching properties and mixing them with the particles.

6 A formulation according to claim 1 and substantially as described herein.